REMARKS

Claims 20, 49, 51, 57, 59 and 65-68 previously were pending in the subject application. Applicants in the present amendment have amended claims 49, 57, 59, and 66-67 and introduced new dependent claim 69. The amended claims now recite that the composition is the composition of claim 68 or 69 instead of the composition of claim 20 or 65, respectively, and that the recited heart or cardiomyocyte is a human heart or cardiomyocyte. New claim 69 depends from claim 65 and requires that the mesenchymal stem cell ("MSC") of the composition is a human MSC.

These amendments are made without prejudice and in order to expedite prosecution. These amendments and the new claim are fully supported at least by paragraphs 0005, 0011, 0013, 0015, 0030, 0032, 0081-0091, 0160-0161, and 0168-0172 of the published application in view of the knowledge of the person of ordinary skill in the art. The new claims do not introduce new matter. Accordingly, Applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 20, 49, 51, 57, 59 and 65-69 will be pending and under examination.

I. Rejections and Responses

The previous rejections for lack of enablement have been overcome and therefore have been withdrawn. *See* Office Action at 4. The previous rejections of claims 20 and 65 for obviousness over Pittenger, Jansen, and Wang have also been withdrawn, the Examiner having found Applicant's arguments in the previous response persuasive. *See id.* at 6. The Examiner has set forth new enablement and obviousness rejections. However, as detailed below, these are also overcome by the amended claims and remarks below.

A. 35 U.S.C. § 112, first paragraph

Rejection

The Examiner has rejected method claims 49, 57, 59, and 66-67 for lack of enablement. *Id.* at 4. According to the Examiner, these claims encompass introducing MSCs derived from

one species into the heart of a different species (xenogeneic transplantation). *See id.* at 3-5. The Examiner ackowledges that the specification enables a method of expressing a functional HCN2 ion channel in the mammalian heart, a method of inducing a pacemaker current in a mammal's heart, and a method of inducing pacemaker current in a cardiomyocyte, where each method entails the use of an autologous or allogeneic mesenchymal stem cell. *See id.* at 3. According to the Examiner, the specification "does not reasonably provide enablement for a method for expressing ion channel or inducing current in the mammal's heart using xenogeneic MSC transplantation." *Id.* at 3.

Response

The enablement rejection does not apply to the rejected claims as currently amended to recite the treatment of a human heart or human cells with a composition comprising human MSCs.

Applicants briefly note that this rejection should be withdrawn even absent the present amendments at least because the rejection hinges on a hypothetical event and that event's hypothetical consequences. As pointed out previously, the Plotnikov reference that the Examiner relies upon merely presents a hypothesis of what might happen if the MSCs were to differentiate. As the Examiner recognizes, "Plotnikov states 'If this [differentiation] occurs, it is reasonable to question whether the cells will maintain their immunoprivileged status.'" Office Action at 5. The Examiner has provided no evidence that differentiation actually does occur or that, if it were to occur, that rejection of the implanted cells would result. At least because the Examiner has made no such showing, this rejection should be withdrawn even without the present amendment.

B. 35 U.S.C. § 103

Rejection

The Examiner has rejected claims 20, 49, 51, 57, 59, and 65-68 as allegedly obvious over U.S. Patent No.7,494,644 ("Lee") and Qu et al. (Circ. Res. 89: e9 (2001), of record). According

to the Examiner, Lee teaches compositions that comprise mammalian cells such as MSCs "genetically engineered to express connexin 43 (Cx43) protein intended for establishing electrical coupling between cardiomyocytes" and the recombinant cells. Office Action at 6-7. According to the Examiner, Lee also teaches a "method of establishing electrical coupling between cardiomyocytes and recombinant mammalian cells" engineered to express Cx43 protein. *See id.* at 7. The Examiner recognizes that "electrical coupling" "allows for intracellular communication" so as to provide for "electrical conduction between the cells." *See id.* The Examiner further states that Lee discloses a method that uses such recombinant cells to "establish an electrical connection between the recombinant cell" and a host myocardial cell in order to treat "a cardiac conduction disturbance in a host." *See id.* The Examiner concedes that Lee does "not disclos[e] MSC comprising nucleic acid encoding HCN2."

According to the Examiner, Qu et al. discloses that treatment of adult and neonatal cells in culture with an "adenoviral construct comprising nucleci acid encoding HCN2" "resulted in expression of high current levels, with faster activation in neonate." *See* Office Action at 8.

The Examiner considers Qu et al. to compensate for the acknowledged deficiency of Lee. According to the Examiner, "it would have [been] obvious for one of ordinary skill in the art to substitute Cx43 with another gene such as HCN2 to produce transformed MSC cells in the method of [sic] disclosed by Lee." The Examiner states that the person of ordinary skill in the art would reasonably have expected such MSCs to form gap junctions when administered to the heart because "Lee taught hMSCs engrafts in the myocardium and forms gap junction with recipient MCS." (To the contrary, as pointed out below, Lee does not suggest that MSCs lacking a Cx43 transgene would form gap junctions. Further, Lee suggests that the transgenically-expressed Cx43 protein makes a critical contribution to the formation of such gap junctions. *See* Lee at col. 3, ll. 25-35 and col. 6, ll. 59-64.)

Response

Claims 20, 49, 51, 57, 59, and 65-68 would not have been *prima facie* obvious because the person of ordinary skill in the art would not have been motivated to modify Lee's disclosure as the Examiner contends. As the Examiner recognizes, Lee teaches "methods for establishing

electrical coupling between cardiomyocytes and recombinant cells which have been genetically engineered to express a connexin protein such as connexin 43 (Cx43) protein." Lee at col. 3, ll. 25-28. Further, Lee's purported "invention is based on the discovery that genetic modification of skeletal muscle cells to express a recombinant connexin, enables the genetically modified cells to establish electrocommunication with cardiac cells via gap junctions." *Id.* at col. 3, ll. 28-32 (emphasis added). Further, according to Lee, "[p]roduction of connexin in the recombinant cell provides for an electrical conection." Lee at col. 11, ll. 1-2.

Lee focuses on the use of skeletal muscle cells for contractility; Lee teaches that such cells should be transformed with connexins to establish electrical connections with cardiac cells. In one embodiment, stem cells can be used but there is no discussion of transfecting the cells with nucleic acids other than those that encode connexins or with any other purpose than to establish electrical connectivity between the transplanted cells and the heart cells. There is no teaching or suggestion to transfect the cells instead with a different nucleic acid, let alone a nucleic acid encoding HCN and a nucleic acid encoding MiRP1, for the purpose of altering pacemaker activity.

Thus, contrary to the pending rejection, the person of ordinary skill in the art would not have been motivated to modify Lee by replacing the Cx43-encoding nucleic acid of the allegedly disclosed compositions and methods with an HCN-encoding nucleic acid. Lee would have discouraged and taught away from the substitution on which the Examiner bases the pending obviousness rejection. This rejection should therefore be withdrawn.

Further, the secondary Qu et al. reference does not cure the deficiencies of Lee, acknowledged by the Examiner to be Lee's failure to teach or suggest the incorporation of an HCN-encoding nucleic acid into the cells introduced into the heart. Qu et al. simply attempts to provide an explanation for the observed phenomenon that "[v]entricular pacemaker current (I_f) shows distinct voltage dependence as a function of age, activating outside the physiological range in normal adult ventricle, but less negatively in neonatal ventricle" even though "heterologously expressed HCN2 and HCN4, the putative molecular correlates of ventricular I_f, exhibit only a modest difference in activation voltage." Qu et al. at e8. The authors conclude

that "the developmental difference in pacemaker current voltage dependence under our experimental conditions is largely accounted for by an effect of the myocyte maturational state on the HCN2 isoform." *Id.* at e12.

Qu et al. thus does not discuss mesenchymal stem cells or their use to deliver genes to the heart or to treat a cardiac rhythm disorder or induce a current in a heart. Specifically, Qu et al. does not teach or suggest that a nucleic acid encoding an HCN can be delivered to a heart via a mesenchymal stem cell. Rather, the only expression experiments discussed by Qu et al. entail infection of rat ventricular myocytes with an adenoviral construct comprising an HCN2-encoding DNA fragment. The deficiency of Lee, recognized by the Examiner, thus is not cured by Qu et al.; Qu et al. would not have motivated the person of ordinary skill in the art to modify Lee to arrive at the claimed compositions or methods. Applicants therefore respectfully request for this additional reason that the rejection of claims 20, 49, 51, 57, 59, and 65-68 as obvious over Lee in view of Qu et al. be withdrawn.

C. Non-statutory Double Patenting

Rejection

The Examiner has provisionally rejected claims 20, 49, 51, 57, 59, and 65-67 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 12, 39, 65, 67-68, and 73-76 of co-pending Application No. 10/342,506 ("the '506 application"), which corresponds to U.S. Publication No. 20040137621, "in view of U.S. Patent No. 6,979,532 ("Jansen et al.").

Response

Applicants request clarification of this rejection to the extent that it is based on, or "in view of," Jansen et al. A non-statutory obviousness-type double patenting rejection may not compare claimed subject matter to the prior art, but rather is limited to consideration of claims in an earlier patent. *See Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1378 n.1 (Fed. Cir. 2003) ("Obviousness compares claimed subject matter to the prior art; nonstatutory double patenting compares claims in an earlier patent to claims in a later patent or application.").

Applicants note that this is a "provisional" rejection over the '506 application, which is not an allowed application. Accordingly, if the now-pending claims of the subject application are otherwise allowable, the present provisional double patenting rejections should be withdrawn and the claims in the subject application should be allowed and issued, whereby the claims of the '506 application would become subject to an obviousness-type double patenting rejection. At that time, applicant will consider filing a terminal disclaimer, if necessary.

CONCLUSION

In view of the remarks made hereinabove, Applicants respectfully request that the Examiner reconsider and withdraw the rejections set forth in the April 29, 2009 Non-Final Office Action, and earnestly solicit allowance of the now pending claims.

If a telephone interview would assist in expediting prosecution of the subject application, the Examiner is invited to telephone the undersigned at the number provided below. No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 11-0600.

Respectfully submitted,

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